REMARKS

Specification Amendments

The specification has been amended at various locations to recite the proper notation for the sequence identifiers.

The specification has also been amended to add two paragraphs at page 6, line 12, directed to physiologically functional equivalents of thrombin derivatives which encompass modifications such as amidation of the carboxyl terminus. Support for the two added paragraphs is found in the specification, for example, at page 8, lines 28-29, which incorporates by reference the entire contents of United States Patent Nos. 5,500,412 and 5,352,664. For the Examiner's convenience, copies of these two patents are enclosed herewith as Exhibits 1 and 2, respectively. This two-paragraph portion is identically recited in both patents and is contained at column 6, lines 35-48 of United States Patent No. 5,500,412 and at column 6, lines 54-68, continuing to column 7, lines 1-2 of United States Patent No. 5,352,664. The term "thrombin derivatives", utilized in United States Patent Nos. 5,500,412 and 5,352,664 has been further clarified in this application to be "thrombin peptide derivatives" for consistency. The present application additionally teaches specific amino acid sequences of thrombin derivatives, such as SEQ ID NO.: 5 (see, e.g., page 7, lines 4-6).

The specification has been further amended at page 5, line 26 and at page 7, line 7, to place the teachings directed to the physiologically functional equivalents of thrombin derivatives as described in the preceding paragraph in additional locations in the specification. The purpose of these amendments is to more readily convey this aspect of the invention to the public. Further to that end, the amino acid sequence of SEQ ID NO.: 5, the thrombin derivative, has been additionally represented as a sequence with an amide at the *C*-terminus in SEQ ID NO.: 6, a physiologically functional equivalent of a thrombin derivative.

No new matter has been added by the amendments to these specification.

New Claims 22-28

Support for new Claims 22-28 is found in the specification, for example, at page 7, lines 4-6; at page 8, lines 28-29, which incorporates by reference the entire contents of United States Patent Nos. 5,500,412 and 5,352,664; and the two paragraphs added at page 6, line 12.

A number of claims have been amended to replace the terms "has" and "having" with "consists of" and "consisting of", respectively. Applicants view the language "has" and "having" in this context as being synonymous with "consists of" and "consisting of", respectively. These changes are intended to make the language of the claims more consistent and definite, and do not narrow the original scope of the claims so amended.

No new matter has been added by the new claims or by the claim amendments.

Paragraph 1: Objection to Claims 7-19

Claims 7-19 have been objected to on the grounds that the claims do not recite the proper notation for the sequence identifiers.

Claims 7-13 and 16-19 have been amended as suggested by the Examiner, thereby rendering this objection of Claims 7-13 and 16-19 moot. Claim 14, which is dependent on Claim 12, and Claim 15, which is dependent on Claim 14, carry the limitations of Claim 12, thereby rendering this objection of Claims 14 and 15 moot.

Paragraphs 2-3: Statutory Double Patenting

Claims 1-4 have been provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of Claims 1-4 of co-pending Application No. 10/050,688.

It is noted that the present rejection is a provisional rejection under 35 U.S.C. § 101. If appropriate, Claims 1-4 will be canceled when there is an indication of allowable subject matter.

Paragraphs 4-5: Obviousness-Type Double Patenting

Claims 1-21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-13 and 17-24 of co-pending Application No. 10/050,688.

It is noted that the present rejection is a provisional obviousness-type double patenting rejection. A Terminal Disclaimer and Certificate Under 37 C.F.R. § 3.73(b) will be filed when there is an indication of allowable subject matter, if appropriate.

Paragraphs 6-7: Rejection of Claims 1-4 Under 35 U.S.C. § 103(a)

Claims 1-4 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Stiernberg, J. *et al.* (*Wound Rep. Reg.*, 8(3):204-215 (2000)) in view of Crowther *et al.* (Distributed at Texas Mineralized Tissue Society, Austin, Texas, August 1998).

Teachings of the Cited References

Stiernberg, J. *et al.*

Stiernberg *et al.* is cited by the Examiner as teaching that "non-proteolytic interaction of thrombin or TP508" "stimulates or activates fibroblasts and is involved in initiation of tissue repair following injury". Paper No. 6, at page 5, lines 13-16. Stiernberg *et al.* is also cited as teaching that TP508 produces the same effect in endothelial, epithelial and fibroblast cells. Paper No. 6, at page 5, lines 16-19. Stiernberg *et al.* is further cited as teaching that "TP508 accelerates tissue repair with a single application at the time of injury." Paper No. 6, at page 5, line 20 to page 6, line 1.

However, as acknowledged by the Examiner, Stiernberg *et al.* do not teach or suggest the use of TP508 in stimulating cartilage growth. Importantly, Stiernberg *et al.* do not teach or suggest that non-proteolytic thrombin cell surface receptors (NPARs) are present on chondrocytes, the primary cell type found in cartilage, or that TP508 can stimulate chondrocyte proliferation and synthesis of matrix proteoglycans.

Crowther *et al.*

Crowther *et al.* do not cure the deficiencies of the Stiernberg *et al.* reference. Crowther *et al.* is cited by the Examiner as teaching that "TP508 can accelerate bone repair". Paper No. 6, at page 6, line 2. It is noted that, in fact, Crowther *et al.* teach that TP508 can accelerate repair of

fresh fractures (acute wounds). Crowther *et al.* do not teach or suggest the use of TP508 in stimulating cartilage growth or repair.

The Combination of References

In support of the rejection, the Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art "to have designed a method of stimulating cartilage growth or repair as set forth in the claimed invention" with a reasonable expectation of success because "Stiernberg et al. teach that non-proteolytic interaction of thrombin or TP508 (agonist of NPAR) stimulates or activates fibroblasts, endothelial, and epithelial cells and initiates wound healing following injury and Crowther et al. teach the acceleration of bone repair with TP508." Paper No. 6, at page 6, lines 3-8. The Examiner alleges that one of ordinary skill in the art would have been motivated to combine the teachings of the references because "both references use TP508 (agonist of NPAR) and Stiernberg et al. teach that a single application of TP508 is effective in accelerating tissue repair at the time of injury not evidenced by the application of growth factors." Paper No. 6, at page 6, lines 9-12. Applicants respectfully disagree that Claims 1-4 are obvious in view of the cited art.

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

As disclosed in the subject application, Applicants have discovered that non-proteolytic thrombin cell surface receptors are present on chondrocytes isolated from articular cartilage and that chondrocytes respond to NPAR agonists. The subject application also discloses results which demonstrate that NPAR agonists can stimulate chondrocyte proliferation and synthesis of matrix proteoglycans. In particular, the application discloses results which demonstrate that chondrocytes express approximately 233,000 thrombin binding sites per cell with apparent affinities of approximately 0.1 nM (3,000 sites) and 27 nM (230,000 sites) and bind to the

thrombin peptide derivative of SEQ ID NO:5 (TP508) (Example 1). Specific results are also disclosed which demonstrate that TP508 can stimulate chondrocyte proliferation and synthesis of matrix proteoglycans (Examples 2A, 2B, 3A, 3B).

Neither of the cited references (Stiernberg *et al.*, Crowther *et al.*), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, neither of the cited references, alone or in combination, would have suggested the use of a NPAR agonist in a method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair with a reasonable expectation of success. As discussed above, Stiernberg *et al.* teach that non-proteolytic thrombin cell surface receptors are present on fibroblasts and epithelial cells and that TP508 can stimulate proliferation of fibroblasts and epithelial cells. Crowther *et al.* teach that TP508 can accelerate repair of fresh fractures. ***Importantly, neither reference teaches or suggests that non-proteolytic thrombin cell surface receptors are present on chondrocytes or that NPAR agonists can stimulate chondrocyte proliferation and synthesis of matrix proteoglycans.*** In fact, prior to Applicants' results described in the subject application, one of ordinary skill in the art would not have reasonably expected to find non-proteolytic thrombin cell surface receptors present on chondrocytes.

Even if one of ordinary skill in the art had known of the presence of NPAR receptors, one still would not have reasonably expected chondrocytes to respond to NPAR agonists. One of ordinary skill in the art would not have reasonably expected NPAR agonists to stimulate chondrocyte proliferation and synthesis of matrix proteoglycans. This is because chondrocytes, which are the primary cell type found in cartilage, are normally quiescent or non-proliferative in cartilage, and have relatively low metabolic rates. Following injury to cartilage, cells in the adjacent undamaged cartilage do not readily migrate into the defect and do not participate to a significant level in the repair process. See, e.g., Chapter 18, "Articular Cartilage Repair and Osteoarthritis", in *Orthopaedic Basic Science: Biology and Biomechanics of the Musculoskeletal System*, 2nd ed., Buckwalter, J.A. *et al.* (eds.) (American Academy of Orthopaedic Surgeons), pages 472-477 (2000); attached hereto as Exhibit 3.

At page 472 of Exhibit 3, it is stated that:

> Because of this limitation, damaged articular cartilage is not restored to a normal condition. Often, once damage is done, it accumulates, leading to a complete loss of the articular surface exposing the underlying bone.

(Chapter 18, "Articular Cartilage Repair and Osteoarthritis", in *Orthopaedic Basic Science: Biology and Biomechanics of the Musculoskeletal System*, 2nd ed., Buckwalter, J.A. *et al.* (eds.) (American Academy of Orthopaedic Surgeons), page 472 (2000)).

Due to the avascular nature of cartilage, these cells would not be expected to see thrombin as an initiator of the repair process.

Accordingly, the teachings of the cited references, either alone or in combination, would not have established, to a reasonable degree of certainty, the use of NPAR agonists in a method of stimulating cartilage growth or repair. The cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of the rejection of Claims 1-4 under 35 U.S.C. § 103(a) are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry and consideration of the IDS are respectfully requested.

Request For Interview

Applicants respectfully request a telephonic interview with the Examiner prior to issuance of the next Office Action.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If

the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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